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Development and evaluation of clopidogrel bisulphatebuccal patch for treatment of thrombosis

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ABSTRACT

Buccal delivery mucoadhesive polymer as their dosage forms should ideally adhere to themucosa and withstands salivation, tongue movement and swallowing for a significant period of time. Moreover, buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in case of toxicity by removing the dosage form the buccalcavity. It is also possible to administer the drug to patients, who cannot be dosed orally to prevent accidental swallowing. Buccal releases of Clopidogrel bisulphate is enabled so that it can be retained in the oral cavity from desired and localize the dosage form in a specific region and control the release rate of drug. Nine batches of Clopidogrel Bisulphate buccal patches were prepared by using three different polymers (HPMC (ESLV), pectin, sodium alginate). Based on the physico-chemical parameters such as appearance, thickness, tensile strength, uniformity of weight, drug content and in vitro diffusion studies H2, P4, and S8 were selected as best formulation. The FTIR graphs of drugs excipients and formulation showed that there is no extra peak or broadening of peaks were observed and thus it indicates that there is no incompatibility between drug and excipients. From the release kinetic results the r^2 value of H2 was found to be higher in zero order release kinetics. In case of korsmeyer peppas model the result indicated that release exponent 'n' value is 0.45<n>0.89. This indicates that the non fickian type (case – II) diffusion mechanism. The amount of drug released are 97.78% of optimized H2 formulation shows a good release. The H2 formulation was subjected to stability studies for 3 months. At the end of three months the H2 formulation showed no significant changes in appearance, colour, texture and drug content at both the room temperature and 40 ± 2ºC & RH 70 ± 5%. From the results, it may concluded that the buccal patches of H2 containing (HPMC – ESLV) in the ratio of 1:6 achieved the objectives of quick release, within 60 sec and accurate dosing (97.78%). Thus, the present study delivers the drug constantly & slowly demonstrated potentials for rapid absorption can be effective therapy, and patient compliance for the treatment of thrombosis.

Keywords: Clopidogrel Bisulphate, buccal patches, Thrombosis, buccal cavity

INTRODUCTION

The novel bioadhesive mucosal dosage forms including adhesive tablets, gels, patches and more recently the use of polymeric films for oral cavity delivery, also known as mouth dissolving buccal patches gained attention in formulation research and growing popularly day by day in the global pharma industry[1].

Oral route has been the commonly adopted and most convenient route for drug delivery. This route has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes, ease of administration as well as traditional belief that by oral administration the drug is well absorbedas the food stuffs that are ingested daily.[2]

The limitations of the most obvious and trusted drug delivery techniques those of the ingested tablet and of the intravenous/intramuscular/ subcutaneous injections have been recognized for some time. The former delivers drug in

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to the blood only through the hepatic system and hence the amount in the blood stream may be much lower than the amount formulated into the tablet. Furthermore liver damage is the unfortunate side effect of many soluble tableted drugs.

An ideal buccal patch should be flexible, elastic and soft yet adequately strong to withstand breakage due to stress from mouth activities. Moreover, it must also exhibit good mucoadhesive strength so that it can be retained in the mouth for a desired duration. As such, the mechanical, mucoadhesive, and swelling properties of buccal patches are critical and essential to be evaluated. The buccal route has high acceptance due to avoidance of 1st pass metabolism and possibility of being accessible for controlled drug release[3].

The aim of the present work is to formulate and evaluate the buccal patches of Clopidogrel Bisulphate for the management of Heart attack, chest pain and stroke.

In recent years, there has been increasing interest in the use of bioadhesive polymers to control the delivery of biologically active agents systemically or locally. These bioadhesive systems are useful for the administrative drugs, which are suspectable to extensive gastro intestinal degradation of drugs, which are susceptible to extensive gastro intestinal degradation and first pass metabolism. Bucolic adhesive system appears to be attractive because it avoids significant limitations of traditional routes of drug administration such as poor absorption, enzymatic degradation and first pass metabolism.[4]

Buccal delivery mucoadhesive polymer as their dosage forms should ideally adhere to themucosa and withstands salivation, tongue movement and swallowing for a significant period of time.[5]

Moreover, buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in case of toxicity by removing the dosage form the buccalcavity. It is also possible to administer the drug to patients, who cannot be dosed orally to prevent accidental swallowing.[6]

Buccal releases of Clopidogrel bisulphate is enabled so that it can be retained in the oral cavity from desired and localize the dosage form in a specific region and control the release rate of drug.[7]

MATERIALS AND METHODS

Preformulation Studies

The preformulation studies which were performing includes

- Description
- Melting point
- Solubility
- Hygroscopic nature
- Identification of drug sample
- Drug – excipients compatability studies

Preparation Of Buccal Patch

Nine batches of drug loaded buccal patch were prepared by using drug with different polymers (HPMC-E5LV, pectin, sodium alginate) in different Drug: Polymer ratio (1:4, 1:6, 1:8) Weighed quantity of polymer was dissolved in calculated quantity of water and heated on awater bath. Calculated amount of drug was added to the above mixture and stirred well until a homogenous mixture was formed. Then calculated amount of permeation enhancer and glycerin were added.

Formulation

Before obtaining the appropriate formulation, various trial were made with respect to solvents, plasticizer and polymer concentration to get a buccal patch having good characteristics like uniform thickness, uniform weight, homogenous drug dispersion and optimum tensile strength. The obtained were visually compared with a commercially available buccal patch matrix diffusion type. When the amount of polymers was less than 0.1g or greater than 0.5g it loses its folding endurance, hence it becomes thick or break with insignificant tensile strength.

Table 1: Formulation of Buccal patch of Clopidogrel Bisulphate

S. No	INGREDIENTS	HPMC (E5LV)			PECTIN			SODIUM ALGINATE		
		H1	H2	H3	P4	P5	P6	S7	S8	S9
1	Clopidogrel bisulphate (mg)	75	75	75	75	75	75	75	75	75
2	Polymer (mg)	300	450	600	300	450	600	300	450	600
3	DMSO (ml)	0.3	0.5	0.7	0.3	0.5	0.7	0.3	0.5	0.7
4	Glycerin (ml)	0.3	0.5	0.7	0.3	0.5	0.7	0.3	0.5	0.7
5	Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Penetration enhancer's incorporation in the Buccal patches

The selection of penetration of enhancers was made on the basis of previous literatureand their miscibility with the solvent employed in the preparation. The concentration and ratio ofenhancers was fixed using the scientific reports and a trial containing drug was prepared and tested for their suitability and drug release.

In-Vitro Drug Release

The *in-vitro* release rate of Clopidogrel Bisulphate buccal patch were evaluated by open ended tube through using phosphate buffer solution pH 6.8 as diffusion medium up to 60 secondsstudies. The cellophane membrane is tied in one

end of the tube and then immersed in the receptor compartment containing 400ml of PBS pH 6.8 which was stirred at medium speed and maintained at 37º C ± 2º C. Samples were withdrawn at regular time intervals and the same volume was replaced by fresh diffusion medium. The samples were analyzed using UV – Visible spectrophotometer (Shimadzu (DM) UV1700) set at 203nm.

Ex-Vivo Study

Ex-vivo buccal permeation studies carried out using Goat buccal skin. The receptorcompartment consisted of 400ml of Phosphate buffer (pH 6.8) in 500ml beaker. Temperature was maintained at 37±0.5ºC and stirred at 900rpm. The cineole strip was placed in Goat buccal skin and tied to the one end of open-ended glass cylinder that was then dipped into freshly prepared phosphate buffer on magnetic stirrer. Samples were taken from receptor medium at 0, 10, 20, 30, 40, 50, 60 sec. Periodically 5ml of sample was withdrawn and some volume of medium was replaced with fresh buffer. All the samples were assayed spectrophotometrically at203nm using PB 6.8 pH as blank. The result shown in Table No:38 & Fig No:44

RESULTS

Compatability studies

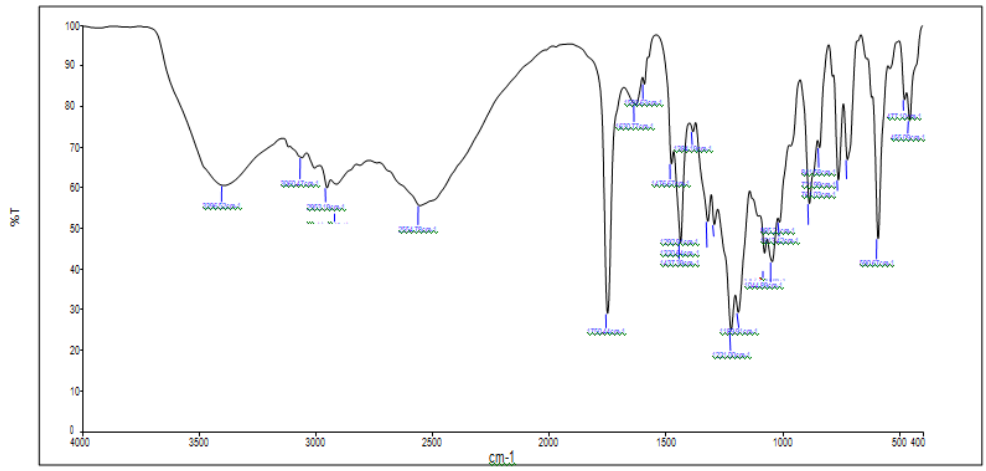

Fig 1: FTIR Spectrum of Clopidogrel bisulphate

Evaluation parameters

Table 2: Physicochemical evaluation of Clopidogrel Bisulphate buccal patch

Formulation	code	Thickness (mm)	Folding enduranceno's	Moisture content (%)	Moisture uptake (%)	Surface pH	Tensile strength (Kg/mm^2)	Uniformity of weight(g)	Drug content (%)	%Elongation (mm)
HPMC (E5LV)	H1	0.18± 0.54	265± 0.08	0.574± 0.62	2.08± 0.56	6.6± 0.07	3.412± 0.07	0.25± 0.75	94.49± 0.07	68± 0.54
	H2	0.26± 0.49	269± 0.58	1.926± 0.6	2.16± 0.09	6.4± 0.12	5.403± 0.67	0.43± 0.3	98.85± 0.67	76± 0.46
	H3	0.27± 0.63	275± 0.85	1.626± 0.07	1.99± 1.05	6.3± 0.25	5.463± 0.85	0.39± 0.47	95.73± 0.70	80± 1.23
Pectin	P4	0.19± 0.17	258± 0.60	1.273± 0.6	2.18± 0.09	7.0± 0.13	3.165± 0.23	0.39± 0.03	95.23± 0.67	75± 0.24
	P5	0.20± 0.85	260± 0.43	1.069± 0.05	2.09± 0.69	6.8.± 0.45	4.563± 0.48	0.28± 0.23	94.09± 0.31	83± 0.74
	P6	0.24± 0.61	265± 0.69	1.133± 0.64	2.07± 0.36	6.9± 0.32	5.412± 0.74	0.29± 0.27	93.95± 0.83	85± 0.94
Sodium alginate	S7	0.13± 0.53	260± 0.42	1.483± 0.47	0.98± 0.43	6.7± 0.9	3.802± 0.22	0.27± 0.4	94.02± 1.06	80± 0.92
	S8	0.19± 0.34	264± 1.5	1.184± 0.10	1.90± 0.21	6.2± 0.32	4.665± 0.91	0.33± 0.63	97.02± 0.49	88± 0.08
	S9	0.21± 0.47	272± 1.0	1.185± 0.03	1.91± 0.04	6.8± 0.29	5.410± 1.65	0.30± 1.28	96.78± 0.72	90± 0.81

Mean ±S.D: n = 3

Table 3: *In-vitro* diffusion profile

Time (sec)	% of drug released								
	HPMC			PECTIN			SODIUM ALGINATE		
	H1	H2	H3	P4	P5	P6	S7	S8	S9
0	0	0	0	0	0	0	0	0	0
10	12.26± 0.02	**14.05± 0.21**	14.19± 0.04	**9.92± 0.37**	12.56± 0.30	14.99± 0.67	9.75± 0.53	**12.08± 0.34**	12.80± 0.38
20	27.78± 0.32	**28.14± 0.02**	27.55± 0.07	**25.75± 0.45**	27.11± 0.49	22.85± 0.42	26.00± 0.01	**29.00± 0.05**	26.35± 0.23
30	42.77± 0.21	**45.70± 0.21**	47.92± 0.70	**41.11± 0.56**	42.87± 0.48	45.00± 0.51	41.02± 0.04	**40.90± 0.07**	44.79± 0.65
40	68.02± 0.36	**69.98± 0.12**	66.09± 0.58	**66.94± 0.40**	68.10± 0.62	63.02± 0.09	60.10± 0.76	**67.03± 0.59**	66.90± 0.76
50	88.08± 1.21	**67.48± 0.05**	85.00± 0.07	**85.94± 0.04**	84.75± 0.53	82.57± 0.21	85.85± 0.03	**83.00± 0.37**	80.89± 0.83
60	95.70± 0.54	**98.86± 0.07**	96.10± 0.04	**95.67± 0.09**	93.10± 0.36	90.45± 0.29	93.90± 0.51	**94.87± 0.40**	92.05± 0.52

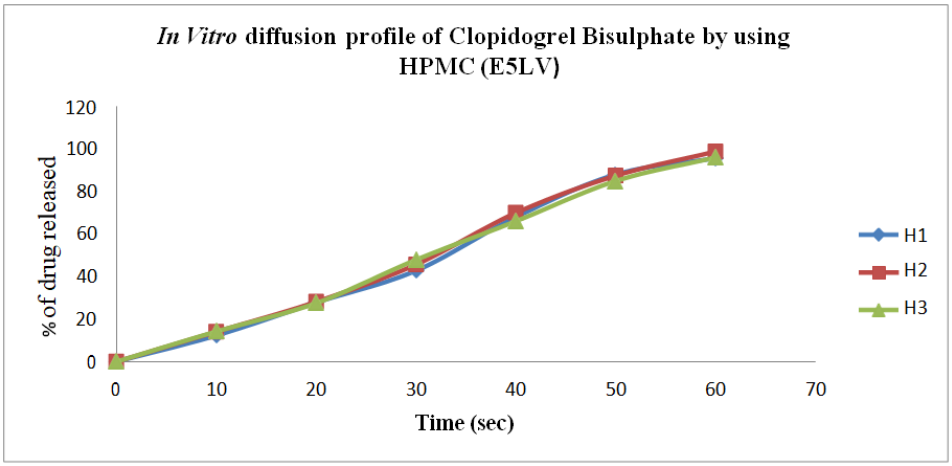

Fig 2: *In vitro* diffusion profile of Clopidogrel Bisulphate by using HPMC

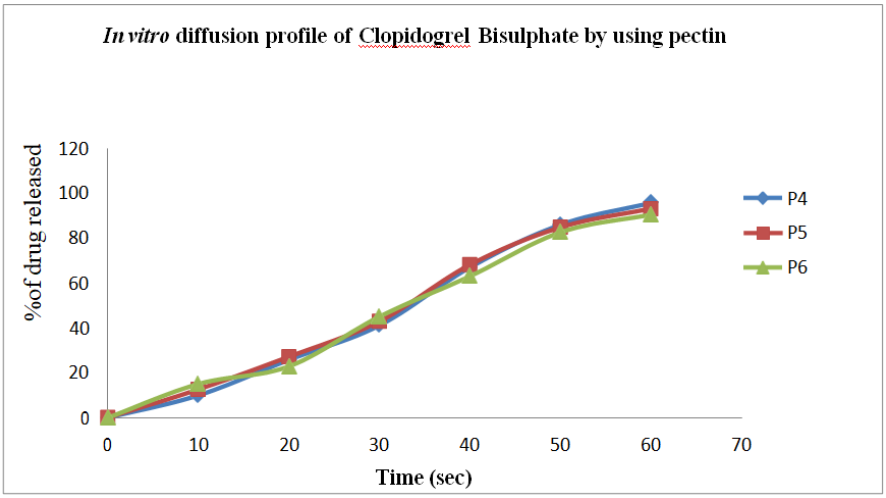

Fig 3: *In vitro* diffusion profile of Clopidogrel Bisulphate by using Pectin

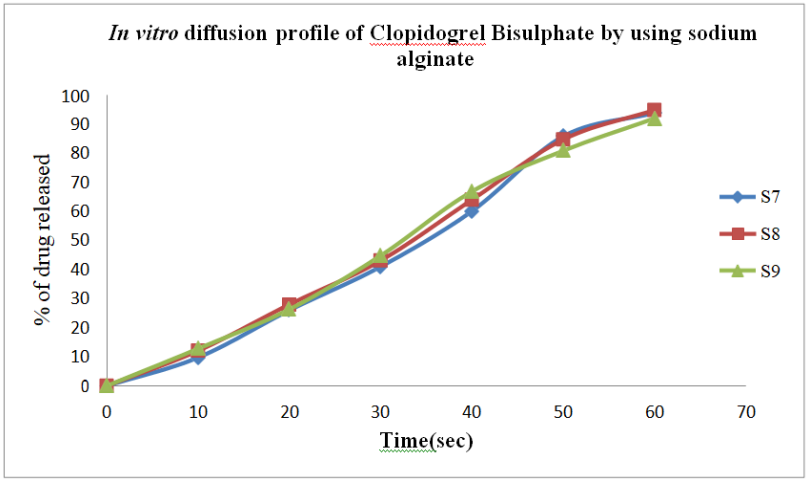

Fig 4: *In vitro* diffusion profile of Clopidogrel Bisulphate by using sodium alginate

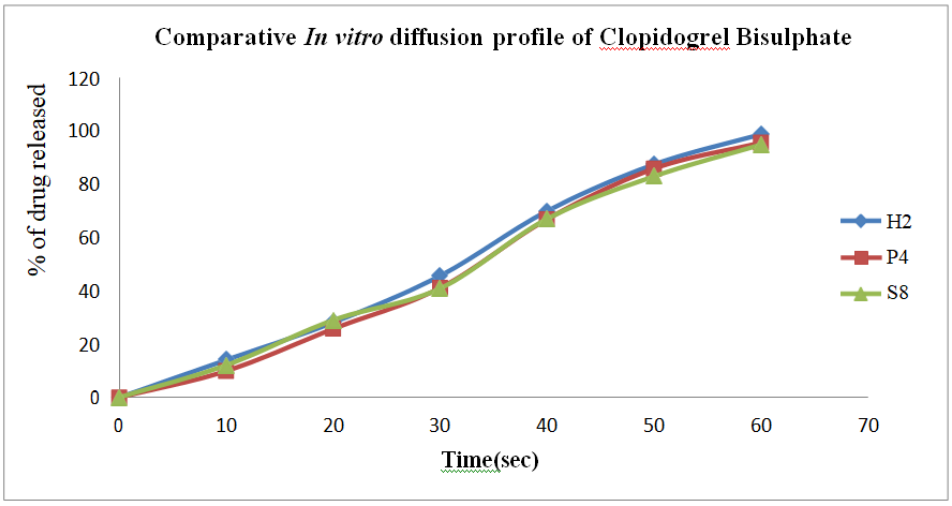

Fig 5: Comparative *In vitro* diffusion profile of Clopidogrel Bisulphate

RELEASE KINETICS

Table 4: Cumulative percentage release of H2 formulation

Timein (sec)	Logtime	√time	% of drug release	Cumulative % of drug release	Log cumulative % of drug release	% of drug remained	Log cumulative % of drug remained
0	0	0	0	0	0	100	2
10	1	14.05 ±0.21	14.06	1.407	1.149	85.95	1.934
20	1.301	28.15 ±0.02	28.15	1.408	1.449	71.85	1.856
30	1.476	45.70 ±0.21	45.70	1.524	1.660	54.3	1.734
40	1.602	69.99 ±0.12	69.99	1.750	1.845	30.01	1.477
50	1.698	67.48 ±0.05	87.49	1.750	1.942	12.51	1.096
60	1.778	98.86 ±0.07	98.86	1.649	1.996	1.14	0.058

Table 5: Cumulative percentage release of P4 formulation

Timein (sec)	Logtime	√time	% of drug release	Cumulative % of drugrelease	Log cumulative % of drug release	% of drug remained	Log cumulative % of drug remained
0	0	0	0	0	0	100	2
10	1	3.163	9.92 ±0.37	0.992	0.997	90.08	1.956
20	1.301	4.471	25.74 ±0.45	1.287	1.411	74.26	1.872

30	1.477	5.478	41.11 ±0.56	1.370	1.614	58.89	1.770
40	1.602	6.324	66.95 ±0.40	1.674	1.826	33.05	1.518
50	1.699	7.071	85.93 ±0.04	1.719	1.934	14.07	1.147
60	1.778	7.746	95.67±0.09	1.595	1.981	4.33	0.635

Table 6: Cumulative percentage release of S8 formulation

Time in(sec)	Logtime	√time	% of drug release	Cumulative % of drugrelease	Log cumulative % of drug release	% of drug remained	Log cumulative % of drug remained
0	0	0	0	0	0	100	2
10	1	3.163	12.08 ±0.34	1.208	1.083	87.92	1.944
20	1.301	4.471	29.00 ±0.05	1.450	1.462	71	1.851
30	1.477	5.476	40.90 ±0.07	1.363	1.612	59.1	1.772
40	1.602	6.324	67.03 ±0.59	1.675	1.825	32.97	1.518
50	1.699	7.072	83.00 ±0.38	1.660	1.918	17	1.230
60	1.778	7.745	94.89 ±0.40	1.583	1.976	5.11	0.708

Table 7: *Ex-vivo* study of Optimized Formulation

Time (sec)	% of drug released
	H2 formulation
0	14.02 ± 0.03
10	28.13 ± 0.28
20	45.67 ± 0.01
30	69.29 ± 0.87
40	87.40 ± 0.40
50	98.69 ±0.05

Table 8: *Ex vivo* Diffusion Profile for H2 Optimized Formulation

Time in(sec)	Logtime	√time	% of drug release	Cumulative % of drugrelease	Log cumulative % of drug release	% of drug remained	Log cumulative % of drug remained
0	0	0	0	0	0	100	2.000
10	1.000	3.161	14.02± 0.03	1.403	1.147	85.98	1.935
20	1.302	4.473	28.13± 0.28	1.408	1.449	71.87	1.858
30	1.478	5.476	45.67± 0.01	1.521	1.660	54.33	1.734
40	1.601	6.325	69.28± 0.87	1.733	1.841	30.71	1.486
50	1.698	7.071	87.40± 0.40	1.747	1.942	12.6	1.100
60	1.779	7.746	98.69±0.05	1.645	1.994	1.31	0.118

Table 9: Descriptive statistic of regression and parameter of the mathematical models for theDiffusion data of formulation H2

Kinetic Models	Statistical parameters	Formulation H2
Zero order	R^2	0.992
First order	R^2	0.864
Higuchi	R^2	0.882
Korsemeyer peppas	R^2	0.995
	n	1.163

Table 10: Result of stability study of Clopidogrel Bisulphate buccal patch (H2)

Parameter	Room temperature	40±2°C & RH 70±5%
Visual Apparatus	Transparent	Transparent
Initial	No change	No change
At the end of 1st month	No change	No change
At the end of 2nd month	No change	No change

At the end of 3rd month	No change	No change
Colour	Dull white	Dull white
Initial	No change	No change
At the end of 1st month	No change	No change
At the end of 2nd month	No change	No change
At the end of 3rd month	No change	No change
Texture	Smooth	Smooth
Initial	No change	No change
At the end of 1st month	No change	No change
At the end of 2nd month	No change	No change
At the end of 3rd month	No change	No change
Drug content (%)		
Initial	97.78 %	97.64 %
At the end of 1st month	97.64 %	97.50 %
At the end of 2nd month	97.45 %	97.40 %
At the end of 3rd month	97.38 %	97.34 %

DISCUSSION[8-10]

The dissolution medium was prepared by using phosphate buffer pH 6.8 the absorption maximum of clopidognel bisulphate was estimated by scanning the drug solution 10mg/ml using UV Double Beam spectro-photometer. The obtained spectrum showed that the x max was reported as 203 nm in phosphate buffer pH 6.8.

Calibration plot of Clopidogrel Bisulphate was plotted at 203nm.The correlation coefficient was found to be r^2 0.9999, which indicated linearity and obeys Beers law within the range of 5-25 mg/ml.

IR studies were carried out for pure drug and excipients, which we used in formulationsto determine the interaction between drug and excipients. The spectral value for the drug was compared with reference standard sample spectra. The IR spectrum of the Clopidogrel Bisulphate showed the characteristics peaks at 1748.81 cm^{-1} (C=O Stretching), 1651.49 cm^{-1} (C=C Stretching), 2126.00 cm^{-1} (C-S-C Stretching), 1219.12 cm-^{1} (C-Cl Stretching chlorophenyl), 1192.29 cm^{-1} (Pyridine ring stretching).The IR Spectrum of the mixture of polymers showed that the characteristics peaks at 3418.14 cm^{-1} (OH stretching), 2930.17cm^{-1} (C-H stretching), 2126.00 cm^{-1} (C-S-C Stretching), 1375.53cm^{-1} (Symmetric O- CH3 bending), 1424.58 cm^{-1} (O-C=O Asymmetric stretching). The spectra of formulations showed presence of peaks in the region of characteristics peaks of drugs confirmed the absence of interactions between the drugs and excipients used in the formulation.

The physico-chemical evaluation of prepared buccal patches from all formulated patched were found to be smooth in texture and transparent. The individual weight of all formulations was determined and the average was calculated as triplicate. It was observed thatthe weight of the patches in each formulation was found to be uniform.

The thickness of the patches of each formulation was determined using vernier caliper. It was observed that the thickness of all patches with increased polymer content showed a marginalincrease in thickness.

The folding endurance was determined as per the procedure mentioned in the methodology. It was found that all the formulations showed good folding endurance > 300.

The surface pH of the patches was also determined and observed that the surface pH of each was found between 6.28±0.36 and which means that they may have less potential to initiate the buccal mucosa as a result patches would be compatible to mucosa.

The percentage drug content of all formulations prepared it was observed that the maximum amount of drug released in all the formulations .The results for all the formulations are given.

The HPMC (E5LV), Pectin, Sodium alginate gives an indication of the strength and elasticity of the patch. A weak and soft polymer is characterised by a low tensile strength (T/S)& percentage elongation (E/B). Hard and brittle polymer shows a moderate TS & low E/B. A soft and tough polymer is characterised by a moderate TS & high E/B. Whereas a hard and toughpolymer shows a high TS & E/B. The results showed that, among the formulation of HPMC (E5LV), Pectin, Sodium alginate, TS & E/B increased with the increase in the percentage of polymers.

From the physio-chemical evaluation of Clopidogrel Bisulphate, buccal patches areprepared by solvent casting method with drug with three different types of polymer ratio such as (1:4, 1:6, and 1:8). From this H2, P4, and S8 the optimized buccal patches were taken further studies. The buccal patches of Clopidogrel Bisulphate buccal patches.

In vitro diffusion studies amongst the formulation H2 containing higher concentration of drug released (98.8 ±0.07). Increased concentrations of H2 resulted the faster drug release. This result was attributed to increased wettability and penetration of water into the patch matrices and hence increased release of drug was tabulated in Table no: 34

In kinetic studies to determine the release mechanism that provides the best description to the drug release, the *in vitro* release data were fitted to zero order, first order & higuchi model. The release data were also kinetically analysed using the korsmeyer – peppas model. The data were processed for regression analysis using MS- EXCEL statistical function. In the present investigation, the release from the polymers followed anomalous behaviour of non-fickian transport mechanism (case – II). As a result, the combination of diffusion and erosion was the mechanism followed by the formulations as the 'n' values ranges from 1.163 as per korsmeyer peppas model, which in turn justified suitability of polymers for the preparation of buccal patches.

Ex-vivo permeation studies was observed that, as the polymer content increased, the percentage drug permeation decreased. The H2 formulation containing better permeation compared to all other formulations. It was found that the results obtained in *ex- vivo* study indicated that drug has the better ability to cross the buccal behaviour at a faster rate.

Stability testing was carried out for all the formulations for a period of 3 months. All the formulations were obtained are evaluated with respect to physical appearance, drug content, surface pH, *in vitro* drug release .The results of stability studies of H2 buccal patches showed no significant change with respect all parameters at the end of 3 months when stored in room temperature and 40 ± 2ºC & RH 70 ± 5%. Ageing did not alter the drug release profiles of any of the patches significantly till the end of the storage period. Buccal patches were found to be physically and chemically stable.

SUMMARY AND CONCLUSION

Nine batches of Clopidogrel Bisulphate buccal patches were prepared by using three different polymers (HPMC (ESLV), pectin, sodium alginate). Based on the physico-chemical parameters such as appearance, thickness, tensile strength, uniformity of weight, drug content and in vitro diffusion studies H2, P4, and S8 were selected as best formulation. The FTIR graphs of drugs excipients and formulation showed that there is no extra peak or broadening of peaks were observed and thus it indicates that there is no incompatibility between drug and excipients. From the release kinetic results the r^2 value of H2 was found to be higher in zero order release kinetics. In case of korsmeyer peppas model the result indicated that release exponent 'n' value is 0.45<n>0.89. This indicates that the non fickian type (case – II) diffusion mechanism. The amount of drug released are 97.78% of optimized H2 formulation shows a good release. The H2 formulation was subjected to stability studies for 3 months. At the end of three months the H2 formulation showed no significant changes in appearance, colour, texture and drug content at both the room temperature and 40 ± 2ºC & RH 70 ± 5%. From the results, it may concluded that the buccal patches of H2 containing (HPMC – ESLV) in the ratio of 1:6 achieved the objectives of quick release, within 60 sec and accurate dosing (97.78%). Thus, the present study delivers the drug constantly & slowly demonstrated potentials for rapid absorption can be effective therapy, and patient compliance for the treatment of thrombosis.

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